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ROI Atlas Generation from Whole Brain Parcellation of Resting State fMRI Data

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Introduction

- Whole brain functional connectivity (FC) analyses require specifying the functionally homogeneous regions of interest (ROIs) to be analyzed.
  - Hand placed ROIs suffer from experimentor bias and error.
  - ROI atlases may not correctly describe functional segregation of the brain.
  - Most clustering methods (ICA, SOM, etc.) identify "networks"; this smooths out detail about the interaction between regions.
- We use spatially constrained n-cut spectral clustering to identify spatially coherent and functionally homogeneous ROIs for FC analyses.
- Different methods for measuring similarity between voxels and combining data across subjects to perform group-level clustering are compared.
- We also explore different methods for estimating the optimal number of clusters and investigate trade-offs associated with this choice.

Methods

Subjects

- 41 healthy volunteers participated in accordance with IRB Policy (18F, age 28.9 +/- 7.2).

Scanning

- 3.0T Siemens Magnetom TIM Trio using 12-channel head matrix.
- Resting state data were acquired with a Z-SAGA sequence [1] to minimize susceptibility artifacts.
  - TR/TE1/TE2/FA/FOV = 3000 ms/30 ms/66 ms/90°/220 mm
- 150 images acquired in thirty 4-mm axial slices, in plane resolution 3.44 mm x 3.44 mm, 7 min scan.
- Subjects were instructed to fixate on a point while "clearing their minds of any specific thoughts".

Preprocessing

- Functional scans were slice timing corrected, motion corrected, written into MNI space at 4 mm x 4 mm x 4 mm resolution and spatially smoothed with a 6-mm FWHM Gaussian using SPM5.
- Data were restricted to gray matter, de-noised by regressing out motion parameters, CSF and WM time-courses and bandpass filtered 0.009 Hz < f < 0.08 Hz.

Spatially Constrained Normalized Cut (ncut) Clustering

- Represent data as an undirected weighted similarity graph, $G = (V, E)$.
  - Vertices, V, correspond to voxels.
  - Edges, E, connect two voxels and are weighted by the non-negative similarity, w_{ij}, between voxels.
  - Spatial coherence is enforced by only connecting a voxel to other voxels in its 3D neighborhood [2].
- The algorithm cuts the graph into a specified number of clusters, K, such that intracluster similarity is greater than intercluster similarity.
- Normalized cut "balances" the sum of edge weights within each cluster.
- Practically, G is represented as an adjacency matrix W of edge weights, w_{ij}, and the ncut problem is solved by linear algebra.
- Ncut clustering was performed using a Python implementation of the algorithm presented in [3].

Similarity can be measured in many ways

- r_t: Pearson correlation between voxel time-courses, threshold $r_t \geq .5$.
- r_s: Pearson correlation between the FC maps generated by voxel time-courses, threshold $r_s \geq .5$.

Two methods for group level clustering

- Average subject specific W matrices, and cluster the results.
- Cluster each individual, combine the results, and cluster again.
  - After clustering each subject, construct an affinity matrix A, where entries $a_{ij} = 1$ if voxels i and j are in the same cluster, $a_{ij} = 0$ otherwise.
  - Average affinity matrices across subjects, and perform ncut clustering on the resulting matrix.

Performance Metrics

LOOCV Reproducibility

- Calculate the similarity between the clustering result from a single subject's data to the result of group level clustering with that subject excluded.
- Variation of Information

$$H(C) = -\sum_{k=1}^{K} P(k) \log P(k) \qquad I(C, C') = \sum_{k=1}^{K}\sum_{k'=1}^{K'} \log \frac{P(k, k')}{P(k)P'(k')}$$

$$VI(C_m, C_{-m}) = H(C_m) + H(C_{-m}) - 2I(C_m, C_{-m})$$

- Dice Coefficient

$$D(C_m, C_{-m}) = \frac{2|C_m \cap C_{-m}|}{|C_m| + |C_{-m}|}$$

Cluster Homogeneity

- Modified Silhouette

$$a_{p,j} = \frac{1}{n_p(n_p - 1)} \sum_{i \in c_p, i \neq j} s(v_i, v_j) \qquad b_{p,j} = \frac{1}{N(N-1)} \sum_{i \notin c_p} s(v_i, v_j)$$

$$si_k = \frac{1}{N} \sum_{p=1}^{k} \sum_{j \in c_p} \frac{a_{p,j} - b_{p,j}}{\max\{a_{p,j}, b_{p,j}\}}$$

Accuracy of Representation

- ROIs chosen in M1, V1, and vPCC to generate FC maps of visual, motor, and default mode networks.
- Pearson correlation calculated between voxel-wise FC maps and cluster-wise FC maps for each subject and various values of K.
- Also performed for the Tailaraich and Tournoux (TT)[4], Automated Anatomic Labeling (AAL)[5], Harvard-Oxford (HO)[6], and Eickhoff-Zilles (EZ)[7] ROI atlases.

Results

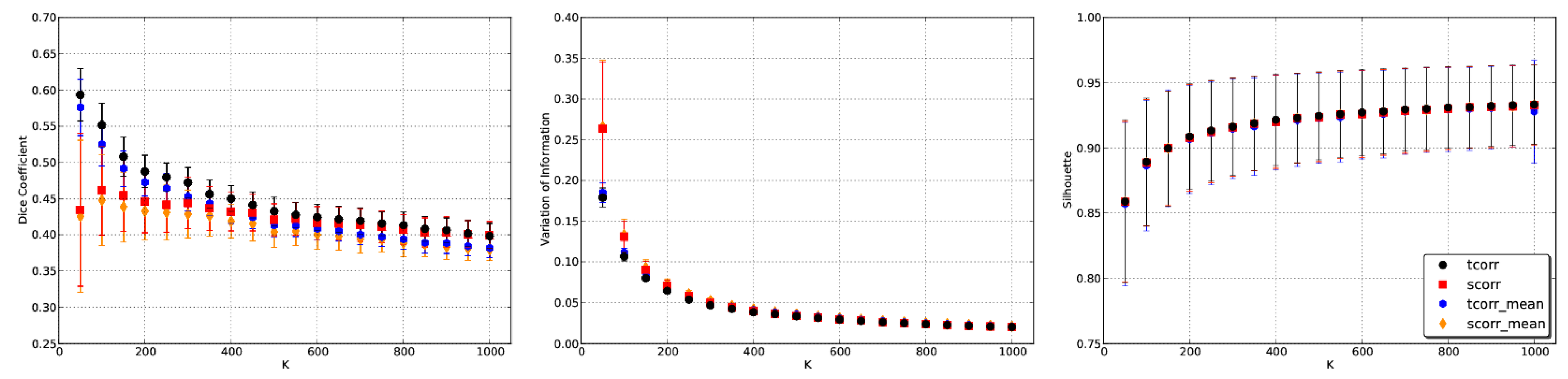

Figure 1: Estimating the optimal number of clusters

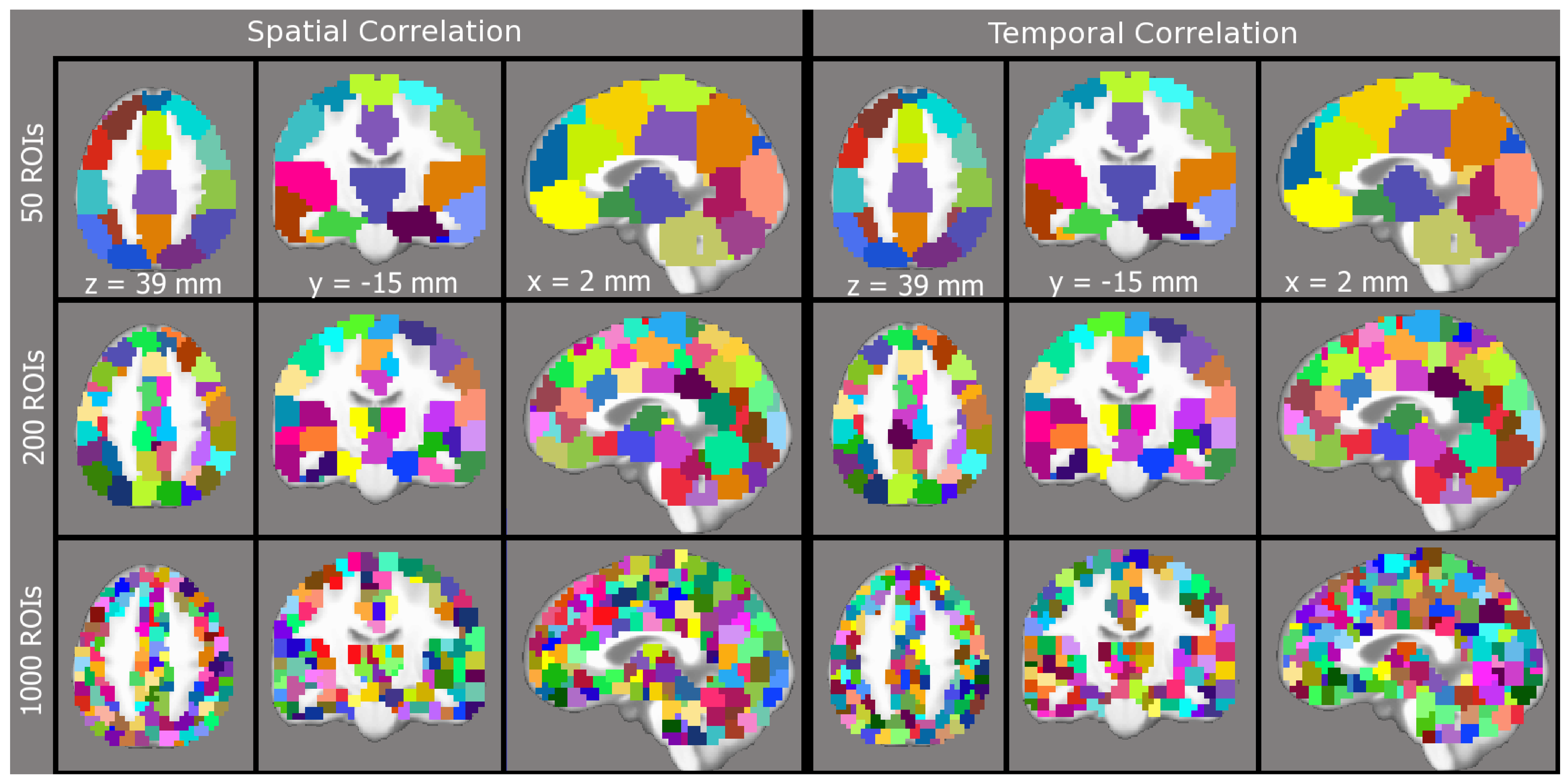

Figure 2: Examples of results for different levels of clustering.

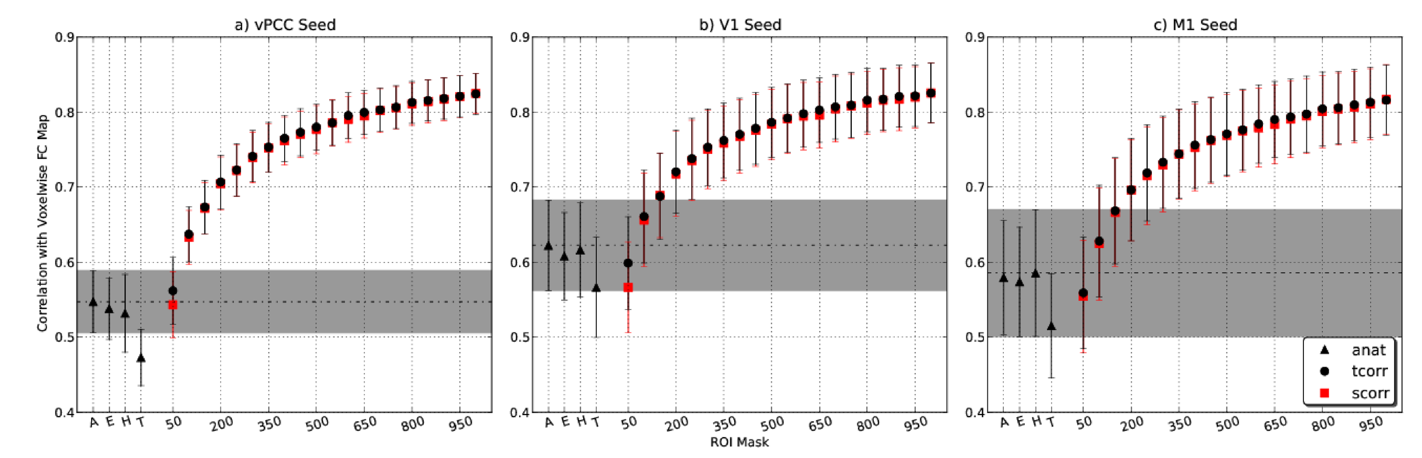

Figure 3: Similarity between voxel-wise FC maps, clustered FC maps, and FC maps generated using anatomical atlases. The horizontal gray bars represents the mean +/- one standard deviation for the best performing anatomical atlas.

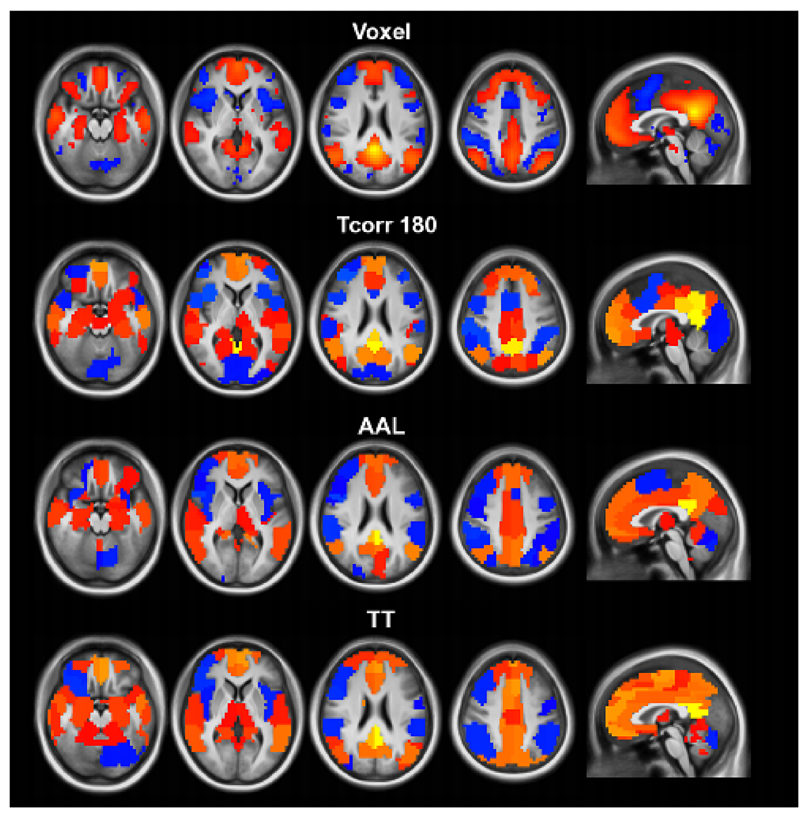

Figure 4: Group averaged default mode network FC maps for voxel, clustering with $K = 180$, TT and AAL atlases.

- As shown in figure 1 cluster improves as K increases, but reproducibility degrades, r_t with two-level group clustering has the best reproducibility.
- In figure 2 results from r_t and r_s are similar, $K = 50$ is underclustered, and the small clusters at $K = 1000$ reduce interpretability.
- Figure 3 shows that the accuracy of representation improves with K, clustering outperforms anatomical atlases for $K > 100$.
- The anatomical atlases perform better for motor and visual networks than they do for the default mode network.
- Figure 4 illustrates that the AAL and TT atlases do not accurately represent the anterior cingulate or frontal cortex components of the default mode network, $K = 180$ captures most of the detail of the voxel analysis.

Conclusion

- Spatially constrained spectral clustering is capable of identifying functionally homogeneous and spatially coherent ROIs for FC analysis.
- Results generated using r_t outperform r_s and the two-level approach performs better than averaging, although the differences are small, and the two-level approach is computationally expensive.
- No optimal choice of K was found, rather it can be chosen to optimize an experiment.
- Clustering results are capable of more accurately representing resting state networks than the explored anatomically derived ROI atlases.

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